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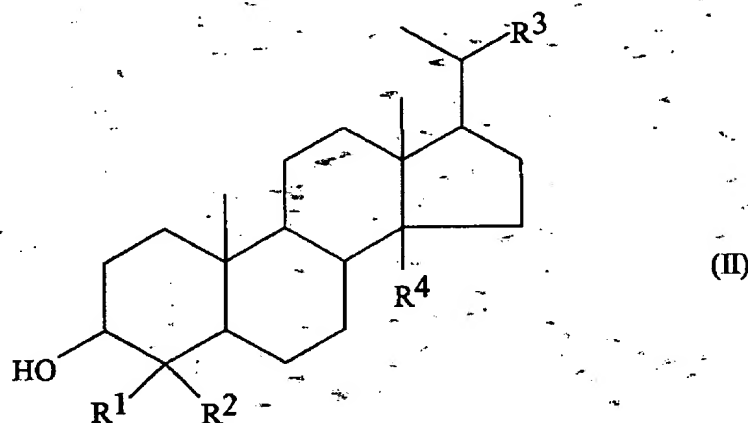
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which optionally have one or more double bonds, but that the Specification lacks a written description of these compounds.

Applicants traverse this rejection and the contentions set forth in support thereof for the reasons set forth below.

To begin with, Applicants' claimed invention is directed to processes for the preparation of sterol phosphates, products thereof, and uses for the same, wherein the process comprising: (a) providing a sterol of the general formula (II), having a fused, four-ring steroidal nucleus;



wherein each of  $R^1$ ,  $R^2$  and  $R^4$  independently represents a hydrogen atom or a methyl group and  $R^3$  represents a linear or branched alk(en)yl group having from 1 to 15 carbon atoms, and wherein the fused, four-ring steroidal nucleus can contain one or more carbon-carbon double bonds; and (b) reacting the sterol with polyphosphoric acid in a non-polar solvent.

In the Specification, the process is described as including the reaction of polyphosphoric acid with a sterol, wherein the sterol may optionally be completely or partially hydrogenated, and wherein the reaction is performed in a non-polar solvent. (See, Applicants' Spec., p. 2, lines 18-21). The sterols which are to be used to produce the sterol phosphates according to the present invention are described in more detail thereafter. As set forth in Applicants' Specification,

Sterols - which may be used as starting materials for the production of sterol phosphates - are understood to be steroids which contain only a hydroxyl group but no other

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functional groups at C-3. Formally, therefore, they are alcohols which would explain why this group of compounds is sometimes also referred to as sterols. Generally, sterols contain 27 to 40 carbon atoms and one double bond in the 5/6 position and optionally in the 7/8, 8/9 or other positions. Besides these unsaturated species, however, other suitable starting materials are the partly saturated or saturated compounds obtainable by complete or partial hydrogenation. (See, Applicants' Spec., p. 3, lines 3-12 (*emphasis added*)).

The detailed description provided in Applicants' Specification, as noted above, explains that various sterol starting materials, with varying degrees and locations of unsaturation are encompassed by the present invention.

One of ordinary skill in the art, upon reading the entire Specification, would readily recognize that the identified double bonds of formula (I) are merely representative of possible unsaturation. It is clear from the detailed description that various degrees of unsaturation, at various location on the steroidal nucleus are encompassed by the present invention. Moreover, Applicants' Specification contains examples (Examples 1-6 in Table 1 at p. 19) which sets forth various sterol starting materials which have different amounts of unsaturation, and in different locations about the sterol molecule.

Accordingly, Applicants respectfully request reconsideration by the Examiner and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

In Paper No. 6, the Examiner rejects claims 21 and 22 under 35 U.S.C. §102(b), as being anticipated by Cremlyn, R., *et al.*, "Some Steroid Phosphates and Related Compounds", J. CHEM. SOC., vol. 17, pp. 2305-10 (1969) (hereinafter referred to as "Cremlyn"). Specifically, the Examiner contends that Cremlyn discloses ergosteryl dihydrogen phosphate and lanosteryl dihydrogen phosphate, citing lines 18 and 27 of the 2<sup>nd</sup> column of page 2309. The Examiner argues that the disclosure of these compounds anticipates the rejected claims.

Applicants strenuously, but respectfully, traverse the Examiner's rejection and the arguments and contentions in support thereof for the reasons set forth below in detail.

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To begin with, in order for a rejection under 35 U.S.C. §102(b) to be proper, each and every element of the claimed invention must be taught, either expressly or inherently, in a single prior art reference. (*See, e.g.*, M.P.E.P. §2131).

One aspect of Applicants' claimed invention, embodied in the rejected claims, is directed to sterol phosphates prepared by the process of claim 10, *i.e.*, reacting the sterol with polyphosphoric acid in a non-polar solvent. Applicants' claimed invention does not involve the use of halogenated sterol compounds such as sterol phosphorodichloridates.

Cremlyn discloses the production of various sterol compounds, including certain sterol dihydrogen phosphates, via the hydrolysis of the corresponding sterol phosphorodichloridates. (*See*, Cremlyn, p. 2305, 2<sup>nd</sup> col., lines 14-24). Cremlyn specifically discloses the simultaneous production of the corresponding sterol chloride as a result of such hydrolysis, and suggests a mechanism for their formation. (*See, id.*, at lines 27-31). Thus, the products of the phosphate production scheme disclosed in Cremlyn contain halogen compounds.

Applicants' claimed sterol phosphates are the products of processes which do not employ phosphorodichloridates, and accordingly, do not contain sterol chlorides resulting from their preparation.

Therefore, Applicants' respectfully submit that the hydrolysis products of Cremlyn are not the same as the claimed sterol phosphates, and that Cremlyn does not teach sterol phosphates according to the processes of claims 10 and 20. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) over Cremlyn.

In Paper No. 6, the Examiner also rejects claims 21 and 22 under 35 U.S.C. §102(b), as being anticipated by Ramirez, F., *et al.*, "Synthesis of Steroid Phosphates via Monomeric Metaphosphate", J. ORG. CHEM., vol. 48, pp. 1417-20 (1983) (hereinafter referred to as "Ramirez"). Specifically, the Examiner contends that Ramirez discloses stigmasterol dihydrogen phosphate and ergosteryl dihydrogen phosphate, citing compounds 5 and 6 of page 1419. The Examiner argues that the disclosure of these compounds anticipates the rejected claims.

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Applicants strenuously, but respectfully, traverse the Examiner's rejection and the arguments and contentions in support thereof for the reasons set forth below in detail.

As described above, one aspect of Applicants' claimed invention, embodied in the rejected claims, is directed to sterol phosphates prepared by the process of claim 10, *i.e.*, reacting the sterol with polyphosphoric acid in a non-polar solvent. Applicants' claimed invention does not involve the use of (1-phenyl-1,2-dibromoethyl)phosphonic acid. Furthermore, Applicants' claimed invention does not produce sterol phosphates containing  $\alpha$ -bromostyrene by-products.

Ramirez discloses a process for preparing sterol phosphates wherein a source of metaphosphate is reacted with a sterol. Ramirez discloses the use of (1-phenyl-1,2-dibromoethyl)phosphonic acid only, because of its ready availability and its convenient rate of decomposition in aprotic solvents such as dichloromethane. (See, Ramirez, p. 1418, "Results and Discussion"). Ramirez discloses a specific synthetic route for the preparation of steroid dihydrogen phosphates wherein (1-phenyl-1,2-dibromoethyl)phosphonic acid is reacted with the dried steroid in a solution of anhydrous dichloromethane. In the disclosed synthetic procedure, Ramirez specifically points out the presence of unwanted  $\alpha$ -bromostyrene by-product in the phosphate product. (See, *id.*, at pp. 1419-20).

Applicants' claimed sterol phosphates are the products of processes which do not employ (1-phenyl-1,2-dibromoethyl)phosphonic acid, and accordingly, do not contain brominated by-products resulting from their preparation.

Therefore, Applicants respectfully submit that the synthetic products of Ramirez are not the same as the claimed sterol phosphates, and that Ramirez does not teach sterol phosphates according to the processes of claims 10 and 20. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) over Ramirez.

Finally, in Paper No. 6, the Examiner rejects claims 10-20 under 35 U.S.C. §103(a), as being unpatentable over Okamoto, Y., "Synthesis of Alkyl Dihydrogenphosphate by the Reaction of Alcohols and Silyl Polyphosphate", BULL. CHEM. SOC. JPN., vol. 58, pp.3393-4 (1985) (hereinafter referred to as "Okamoto"), in view of Cremlyn or Ramirez. Specifically, the Examiner contends that Okamoto discloses the synthesis of alkyl dihydrogen phosphate by reaction of an alcohol, such as cholesterol, with a polyphosphate. Additionally, the Examiner

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contends that Cremlyn and Ramirez teach other alcohols, such as ergosterol, lanosterol and stigmasterol, and phosphates thereof.

The Examiner argues that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have utilized "any alcohol" in the process of Okamoto with a reasonable expectation of obtaining the desired phosphates. On this basis, the Examiner argues that the claimed invention is obvious.

Again, Applicants strenuously, but respectfully, traverse the Examiner's rejection, and the arguments and contentions in support thereof, for the following reasons.

It is well-settled that where a combination of references is used to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation to modify or combine the references as suggested by the Examiner (it is not sufficient to say that the cited references can be combined or modified without a teaching in the prior art to suggest the desirability of the modification); (2) there must also be a reasonable expectation of success; and (3) the references as combined must collectively teach or suggest all limitations of the claims. The teaching or suggestion to combine and modify the cited art and the reasonable expectation of success must both be found in the prior art and not in Applicants' Specification. (M.P.E.P. §2143).

Applicants' claimed invention is directed to processes for the preparation of sterol phosphates, wherein the process comprising: (a) providing a sterol of the general formula (II), and (b) reacting the sterol with polyphosphoric acid in a non-polar solvent.

None of the cited references teaches or suggests the use of polyphosphoric acid for the preparation of sterol phosphates. Furthermore, none of the cited references teaches the reaction of a sterol and polyphosphoric acid in a nonpolar solvent. Okamoto teaches the reaction of an alcohol with trimethylsilyl polyphosphate. Cremlyn employs the hydrolysis of halogenated sterols such as cholesterol phosphorodichloridate. Ramirez uses brominated reagents which produce bromo-by-products.

None of the cited references, nor a combination thereof teaches the claimed process of reacting a sterol with polyphosphoric acid in a nonpolar solvent. Moreover, there is no teaching or suggestion in any of the cited references which would motivate one of ordinary

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skill in the art to make such modifications to the teachings of the references. Absent any teaching or suggestion of each and every element, and given that there is no motivation to modify the references to arrive at the claimed invention, it cannot reasonably be argued that one of ordinary skill in the art would expect to successfully achieve the claimed invention.

Thus, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness based on the cited references, as none of the three criteria necessary to establish such a *prima facie* case of obviousness has been satisfied. Therefore, Applicants respectfully request that the Examiner withdraw the rejection of the claims under 35 U.S.C. §103(a).

In view of the remarks set forth above, Applicants submit that all pending claims patentably distinguish over the prior art of record and known to Applicants, either alone or in combination. Accordingly, reconsideration, withdrawal of the rejection and a Notice of Allowance are respectfully requested.

Respectfully submitted,

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February 14, 2003  
(Date)

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